REMARKS

The specification has been amended to correct the omission of US Patent Application Numbers in paragraph [0186]. In addition, an amended abstract containing less than 150 words has been submitted. The amendments to the specification do not constitute new matter and the amended abstract should in no way be construed as a narrowing of the scope of the subject matter claimed.

Claims 1-3, 7, 9-14, 16-17, and 33-42 are pending in this application. Claims 4-6, 8, 15, 18-26, and 29-32 have been canceled without prejudice. Applicants have amended claims 1-3 and 11. Applicants have amended claim 27 to correct dependency as required by the Examiner. New claims 33-42 have been added. Support for the amendments and new claims can be found throughout the specification for example at: paragraphs [034], [039], [042], [056], [0102], [0107], [0136], [0255], [0272], [0290], and Section 6.8.2.

Applicants reserve the right to pursue the subject matter of the canceled claims in a related application(s), without relinquishing the scope of the claimed subject matter.

The Examiner's First Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn:

On page 3, the Examiner has rejected claims 1-3, 7, 9-14, 16, 17, and 27-28 as allegedly not complying with the enablement requirement. Specifically, the Examiner contends that the specification does not reasonably provide enablement for a method of treating a non-neoplastic hyperproliferative cell or excessive cell accumulation disorder in a patient comprising administering a therapeutically effective amount of an EphA2 agonistic agent, wherein said disorder is lung fibrosis. Applicants respectfully disagree.

The legal standard for the test for enablement is whether one of ordinary skill in the art could make and use the invention without undue experimentation, based on the teachings in the disclosure of the patent specification coupled with information that was known in the art at the time the patent application was filed see (U.S. v. Teletronics Inc., 8 USPQ2d 1217, Fed. Cir 1988).

Factors to be considered in determining whether experimentation is undue include: the breadth of the claims; the nature of the invention; the state of the prior

art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a), citing *In re Wands*, 858, F.2d 731, 737 (Fed. Cir. 1988).

No single factor is controlling, and the Examiner must consider all of the evidence related to each of the factors. MPEP § 2164.01(a). For example, the quantity of experimentation is merely one factor to be considered in determining whether experimentation is undue. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." MPEP § 2164.06, citing *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." MPEP § 2164.06, citing *In re Wands*, 858 F.2d at 737 and *In re Angstadt*, 537 F.2d 489, 502-504 (CCPA 1976).

In addition, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. The Examiner is given the guidance that undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the relevant art at the time of filing. *Fields v. Conover,* 170 USPQ 276, 279 (CCPA 1971). Indeed, the Court of Customs and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), at 218-219:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act. *Id.* at 219.

Accordingly, the law does not require the scope of enablement provided by the specification to mirror precisely the scope of protection sought by the claims. See *In re Fisher*, 166 USPQ 18,24 (C.C.P.A. 1970); see also In re Wright, 27 USPQ2d 1510

(Fed. Cir.1993). To be enabled, all the law requires is that the scope of enablement provided by the specification bear a "reasonable correlation" to the scope of the claims. Moreover, even if evidence to doubt the proposed correlation exists, "the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Thus, to support a non-enablement rejection, the Examiner must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate the teaching in the specification across the entire scope of the claims.

In addition, the Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367,369 (CCPA 1971);MPEP § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support.

Thus, all that is required is that a reasonable amount of guidance with respect to the direction of the experimentation is provided; reasonable certainty with regard to the outcome of the experimentation is not required.

Complete predictability of success of experimentation is not required under the law. Although the Examiner has provided publications that attempt to refute the predictability of using cell lines, those very publications are an indication of just how frequently cell lines were (and are) used by those of ordinary skill in the art at the time of filing. Results obtained by the use of cell lines are not meant to provide a prediction of complete success. Rather, the results obtained by using cell lines provide guidance, not just to the inventor, but also to those of ordinary skill in the art at the time of filing, for practicing the claimed invention. This guidance, in some ways a stepping stone, allows one of ordinary skill in the art to further practice the claimed invention. In some instances, no additional experimentation will be necessary. However, in many instances, additional experimentation, *albeit routine*, will be needed. Regardless, as long as clear guidance is given to one of ordinary skill in the art such that only routine experimentation is necessary to practice the claimed invention, the enablement requirement is satisfied. This is clearly the case with the present application. Even if, *arguendo*, the use of cell lines were not a *perfect* predictor of outcome in primary cells or in animals, Applicants would point out that

subsequent use in primary cells and/or animals would have been merely a routine next step for one of ordinary skill in the art.

The Examiner alleges that reliance on an *in vitro* model of fibrosis fails to enable the treatment of fibrosis with an EphA2 agonistic agent *in vivo*. Applicants respectfully disagree and emphasize that the specification and state of the art at the time of filing demonstrate:

I. An art accepted model of fibrosis, the bleomycin-induced fibrosis model, existed;
II. EphA2 is associated with fibrosis;
III. Agonizing EphA2 is a treatment for fibrosis.

Applicants respectfully submit that the present invention recognizes and demonstrates that EphA2 agonistic agents, such as EphA2 agonistic antibodies, are capable of reducing or ablating a pathology-causing cell phenotype associated with lung fibrosis. Applicants further submit that the instant specification coupled with information known as of the filing date of the present application provides sufficient guidance to enable one of skill in the art to practice the claimed methods without undue experimentation.

I. An art accepted model of fibrosis, the bleomycin-induced fibrosis model, existed

The specification recognizes that the art accepted bleomycin-treated lung epithelial model of fibrosis replicates the key pathologic features of human lung fibrosis, including fibroproliferation and other pathologic conditions as referenced by the citation of Dunsmore and Shapiro, 2004, J. Clin. Invest. 113:180-182 and Kuwano, et al., 1999, J. Clin. Invest. 104:13-9, in paragraph [0019] of the specification. In further support of the bleomycin-treated lung epithelial model, Applicants demonstrate that bleomycin treatment induces the release of IL-8 and IL-6, inflammatory mediators known to facilitate fibrosis progression (see Figures 12 and 13 of the instant specification).

The Examiner alleges that Chua et al. (Am J Respir Cell Mol Biol, 2005, 33:9-13, hereinafter as "Chua") discounts the use of the bleomycin model of fibrosis and supports the contention that treatment of fibrosis is unpredictable. Applicants respectfully disagree. Chua teaches the acceptance and the importance of the bleomycin induced fibrosis model in the understanding of the pathology of lung fibrosis. For example, Chua states "...these studies have also helped characterize

changes in extracellular matrix gene expression during fibrotic development, as well as the physiologic abnormalities that accompany pulmonary fibrosis." (see page 12 1st column, 4th paragraph). Also, Chua states "Other histologic characteristics of bleomycin-induced pulmonary fibrosis also bear resemblance to lesions in human fibrotic lung disease" (see page 12 1st column, 5th paragraph). Furthermore, Chua states "The strengths of the bleomycin model lie in its robust reproducibility and versatility of a scaled-down model of general pulmonary fibrosis" (see page 12, 2nd column, 2nd paragraph). The statements by the authors of Chua symbolize a clear validation of the bleomycin-induced fibrosis model as representative of the related human condition of pulmonary fibrosis at the time of filing of the present application. Chua only suggests that in an effort to understand processes other than the biological processes involved in the pathogenesis of pulmonary fibrosis (of which the bleomycin-induced fibrotic model has contributed greatly), "efforts to develop even better models of the disease continue to be prioritized" (see page 12, 2nd column, 4th paragraph).

The Examiner also alleges that the treatment of lung fibrosis is quite unpredictable in view of Wang et al. (Biochemical Pharmacology, 60:1949-1958, 2000, hereinafter "Wang"). Applicants respectfully disagree. Wang teaches the effectiveness of anti-integrin α4 in the treatment of bleomycin-induced fibrosis in mice. In fact, the authors in Wang use the positive data from these studies in bleomycin-induced fibrosis in mice to suggest that "use of anti-α4 antibody offers therapeutic antifibrotic potential *in vivo*". Clearly, experiments in the art accepted model of bleomycin-induced fibrosis are consistent with the desired outcome of treating a human patient with fibrotic disease.

In addition, Applicants respectfully draw the Examiners' attention to U. S. Patent No.: 7,172,757 entitled "Method Of Treating Fibroproliferative Disorders" (hereinafter referred to as '757), filed June 26, 2003, U.S. Patent No. 6,893,637 entitled "Method Of Treating Fibrosis", filed October 23, 2000 (hereinafter referred to as '637), and U.S. Patent No. 6,652,856 entitled "Methods Of Treating Fibrosis" (hereinafter referred to as '856), filed February 1, 2002. Each of the aforementioned patents discloses and relies on the bleomycin-induced fibrosis model in the representative examples to support the method of treatment claims of each patent. Applicants would respectfully point out to the Examiner that, in addition to the references cited and already discussed herein, the above-mentioned patents were part

of the state of the art at the time of filing. Accordingly, it is abundantly clear that the bleomycin-induced model was a well accepted model for fibrosis in the art at the time of filing.

II. EphA2 is associated with fibrosis

The instant specification teaches that EphA2 is expressed in adult epithelia and provides a specific example demonstrating EphA2 expression in adult lung epithelium tissue samples (see for example, Example 6.5 of the instant specification). Applicants correlate EphA2 upregulation with the onset of lung fibrosis in Example 6.8 of the instant specification using the art accepted bleomycin-induced fibrosis lung epithelial model. In this Example, lung epithelial cells (Beas-2B) demonstrate upregulation of EphA2 expression after treatment with bleomycin (See Figure 17 of the instant specification). Applicants further demonstrate that upregulation of EphA2 in cells leads to morphological changes which mimic changes seen in bleomycin-treated epithelium (See Example 6.8, Figure 7 of the instant specification).

Applicants provide further support for a role of elevated EphA2 expression in the progression of fibrosis by demonstrating that cells with increased levels of EphA2 showed increased levels of fibronectin expression (see Example 6.8 and Figure 8 of the instant specification). The increase in fibronectin expression leads to excess deposition into the extracellular space, another key pathological phenotype of fibrosis. Accordingly, Applicants have demonstrated the association of upregulated EphA2 with the onset of fibrosis.

III. Agonizing EphA2 is a treatment for fibrosis

Using the finding that EphA2 is associated with fibrosis in the bleomycin-induced model, Applicants have demonstrated that agonizing EphA2 is a treatment for fibrosis. Specifically, Applicants have demonstrated that agonistic EphA2 agents readily stimulate the degradation of fibronectin. In the experiment represented by Figure 9, cells are treated with an agonistic EphA2 agent (agonistic EphA2 antibody B13). The Western Blot analysis of cellular extracts demonstrated that the cells treated with an agonistic EphA2 agent (anti-EphA2 antibody, B13) showed a specific degradation of fibronectin over a 24 hour compared to a control protein (paxillin). In addition, the experiment also demonstrated another aspect of the current invention, namely the downregulation of EphA2 expression in response to an agonistic EphA2

agent. Thus, Applicants, through the working examples of the present specification, demonstrated the presence of EphA2 in adult lung epithelium, the upregulation of EphA2 in lung fibrosis, the EphA2 dependent regulation of fibronectin, and the increase of EphA2 degradation upon treatment with an agonistic EphA2 agent.

The Examiner further contends that the treatment of disease with antibodies *in vivo* is generally unpredictable. In support of this contention, the Examiner has cited White et al. (Ann Rev Med 52:125-145, 2001, hereinafter referred to as "White"), which discloses that "only in recent years have some monoclonal antibodies provided sufficient efficacy as therapeutic agents" (see abstract). Applicants respectfully disagree. Applicants assert that the specification also provides clear guidance to the ordinary artisan regarding methods of treating patients with lung fibrosis with agonistic EphA2 agents. The specification teaches the target patient population (Section 5.4.1), therapeutic methods (section 5.4), pharmaceutical compositions (Section 5.7), and dosages of agonistic EphA2 agents, including agonistic antibodies (Section 5.6).

In addition, Applicants respectfully draw the Examiners' attention to the fact that administration of antibodies was well known in the art at the time of the Applicant's claimed invention. It was well known as of the filing date that a large number of antibody therapeutics were already in preclinical trials and in clinical use as evidenced by Reichert et al. (Nature Biotechnology 23(9):1073-1078, 2005, hereinafter "Reichert"), attached as Exhibit A. Reichert reviews antibody products in the clinic and states that between the years 1980 and 2000, **186** monoclonal antibody products had entered clinical trials (see, for example, Table 1). In addition, **17** monoclonal antibodies were FDA approved prior to the filing date of the present specification (see Table 1). Further still, Wang teaches that fibrosis can be treated *in vivo* with the administration of antibodies (see above for discussion). Thus, in contrast to the Examiner's contention, the skilled artisan did possess extensive knowledge in the field of antibody technology, particularly related to the administration of an antibody for clinical effect, at the time the filing of the present application.

Applicants also respectfully draw the attention of the Examiner to U.S. Patents: 7,175,844 entitled "Methods Of Modulating Fibrosis", filed July 17, 2001 (hereinafter referred to as '844), the '757 patent and the '637 patent (each discussed

herein above). Each of the aforementioned patents disclose and claim methods of treating fibrosis with antibody therapeutics, and provide working examples which solely rely on *in vitro* data. Moreover, Applicants submit that the '856 (discussed above), issued November 25, 2003, provides comprehensive disclosure and guidance to the ordinary artisan regarding how to adapt the bleomycin-induced fibrosis model for use in an *in vivo* setting. The '856 patent constitutes a readily available teaching, at the time of filing, of how one of skill could perform a study of an antibody agent in the bleomycin-induced fibrosis model *in vivo*. Again, Applicants respectfully point out to the Examiner that these patents are part of the state of the art at the time of filing. Accordingly, the claims of Applicants' present application as presented should be found fully enabled based on the guidance and working examples presented in the instant specification.

Furthermore, Applicants respectfully draw the attention of the Examiner to the Board of Patent Appeals and Interferences (BPAI) decision of *Ex Parte Boutin*, No. 2006-1879, decided Sept 28, 2006 (hereinafter "*Ex Parte Boutin*") in which the panel reversed the rejection of non-enablement that was applied to the patent application. Claim 1, a representative claim at issue, was directed to a "method for the transfer of a nucleic acid composition to cells." The patent application disclosed working examples of delivery of nucleic acid material to cells in both *in vitro* and *in vivo* settings. However, the Examiner concluded that the claimed method of transferring nucleic acid material to a cell was enabled for *in vitro* but not for *in vivo* applications because the working examples did not demonstrate a therapeutic effect associated with the delivery of nucleic acid material *in vivo*. In the discussion of the reversal, the Board cited *CFMT Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) which states "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect". The Board also stated that "[w]e do not agree with the examiner that enabling the instant claims requires enabling therapeutically effective gene therapy". Moreover, the Board stated that "while the claims rely on gene therapy methods, they do not require producing a clinically effective therapeutic response." Citing *In re Cortright* 165 F.3rd 1353, 49 USPQ2d 1464 (Fed Cir. 1999) in which claims to a method of "treating scalp baldness" could be enabled even if the method did not produce a full head of hair.

This decision is of particular relevance to the present application. The specification of the present application presents working examples demonstrating the association of EphA2 expression with fibrosis, the correlation of EphA2 activity with the progression of fibrosis and the reduction of fibrosis with agents that agonize EphA2 activity *in vitro*. The instant claims recite "a method of reducing fibrosis" with specific limitations; they do not contain any limitation to a perfected commercially viable embodiment as discussed in *CFMT* or a complete therapeutic result as in *Cortright*. Accordingly, based on the disclosure and teachings in the present application, the pending claims are indeed fully enabled.

Applicants further respectfully draw the attention of the Examiner to the Board of Patent Appeals and Interferences (BPAI) decision regarding of *Ex Parte Forstova*, No. 1998-0667, heard Apr 11, 2002 (hereinafter "*Ex Parte Forstova*"), in which the panel reversed the rejection of non-enablement applied to the patent application. Claim 2, a representative claim at issue, was directed to a "method of transferring material into a host cell wherein the biological functioning of the exogenous material in the host cell has a therapeutic effect on a multi-cellular organism containing that cell." The patent application at issue disclosed working examples of successful transfer of genetic material to human cells *in vitro*. The Examiner contended that because the claimed methods read on the field of gene therapy, the claims were not enabled. In the discussion of the rejection, the Examiner expressed concern that the entire field of gene therapy itself was non-enabled as opposed to the use of the presented technology in the field. In *Ex Parte Forstova*, the Board reversed citing *In re Brana* (cited above) which states:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The state at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In the reversal of the non-enablement rejection, the Board stated that "a number of quotes relied upon by the examiner from the references refer to problems or obstacles in delivering the therapeutic to the target in a clinical setting. However,

as stated in *Brana*, that is not the standard for enablement and/or utility". While the claims in *Brana* relate to chemical compounds useful in the treatment of cancer, and the claims in *Ex Parte Forstova* relate to methods of delivering material to cells, Applicants assert that these principles clearly apply to the claims in the instant application.

This is yet another decision of particular relevance to the present application. In the present rejection, the Examiner cites multiple references in the contention that successful *in vivo* treatment of a disorder with an antibody therapeutic is not enabled. As discussed in *Ex Parte Forstova*, referencing *Brana*, this is not the standard for enablement. In the present invention, Applicants have provided data demonstrating the association of EphA2 expression with fibrosis, the correlation of EphA2 activity with the progression of fibrosis and the reduction of fibrosis with agents that agonize EphA2 activity. In other words, Applicants have enabled a method of reducing fibrosis as claimed. Moreover, as discussed above, Applicants have demonstrated that clinical use of antibodies was well established at the time of filing. Accordingly, Applicants have met the standard of enablement and the rejection should be withdrawn.

The Examiner's Second Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn:

On page 7 of the Office Action, the Examiner has rejected claims 11 and 13 for allegedly failing to comply with the enablement requirement. Specifically, the Examiner states that specification provides insufficient direction or guidance regarding how to produce antibodies with less than a full complement of CDRs (6) in the proper orientation. Applicants respectfully disagree.

The Examiner cites Rudikoff et al. (Proc Natl Aca Sci 1982, 79:1979-1983, hereinafter "Rudikoff") as evidence that minor changes, even single amino acid substitutions of the variable regions of antibodies may affect antigen-binding functions. Rudikoff published at least **21 years** prior to Applicants' effective filing date. Rudikoff is thus not at all indicative or representative of the state of the art at the time of Applicants' invention. Therefore, Rudikoff provides no evidence whether, at the time of Applicants' invention, it would have been routine for one of skill in the art to produce an isolated Ab from a second Ab.

Solely in an effort to expedite prosecution, Applicants have amended claim 11 to recite the specific antibodies. Applicants also submit that the rejection based on claim 13 is moot in view of the amendment of claim 11.

Further, on page 8 of the Office Action, the Examiner states that it is not clear from the disclosure that the deposits of Eph099B-102.147, Eph099B-208.261, Eph099B210.248, or B233 meet all the criteria set forth in MPEP 2410.02 items 1-3. Applicants have prepared and submit herewith a declaration and a copy of the receipts of deposit from ATCC regarding the above-mentioned entities (see attached).

CONCLUSION

Applicants respectfully request that the remarks of the present Response be entered and made of record in the present application. The application is believed to be in condition for allowance. Early notice to that effect is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below. If any additional fees are required in connection with this paper, please charge Deposit Account No. 500479 for the appropriate amount.

Respectfully submitted,

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